DOI:
10.1016/j.eururo.2018.10.025

Document Version
Peer reviewed version

Reasons for discontinuing active surveillance: Assessment of 21 centres in 12 countries in the Movember GAP3 Consortium

Van Hemelrijck M[1], Ji X[2], Helleman J[3], Roobol MJ[3], Van der Linden W[4], Nieboer D[3], Bangma C[3], Frydenberg M[5], Rannikko A[6], Shiong LL[7], Gnanapragasam V[8], Kattan MW[2], Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) consortium[a]

1. Translational Oncology & Urology Research (TOUR), School of Cancer and Pharmaceutical Sciences, King's College London, London, United Kingdom
2. Department of Quantitative Health Sciences, Cleveland Clinic
3. Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands
4. Department of Professional Health Solutions & Services, Philips Research, Eindhoven, The Netherlands
5. Department of Surgery, Monash University; Department of Urology, Monash Health
6. Helsinki University and Helsinki University Hospital, Helsinki, Finland
7. Department of Urology, Singapore General Hospital, Singapore
8. Academic Urology Group, Department of Surgery and Oncology, University of Cambridge, Cambridge, UK

a. The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) consortium members presented in Appendix A.

Corresponding author: Dr Mieke Van Hemelrijck
TOUR – King's College London
Guy's Hospital, 3rd floor Bermondsey Wing, London SE1 9RT, UK
Mieke.vanhemelrijck@kcl.ac.uk
020 7188 5594

Email addresses co-authors: JIX@ccf.org; j.helleman@erasmusmc.nl; m.roobol@erasmusmc.nl; wim.van.der.linden@philips.com; d.nieboer@erasmusmc.nl; c.h.bangma@erasmusmc.nl; Antti.Rannikko@hus.fi; lee.lui.shiong@sgh.com.sg; vjg29@cam.ac.uk; kattanm@ccf.org

Word count: 285 (abstract) and 2,710 (manuscript)

Key words: prostate cancer; active surveillance; discontinuation; worldwide

Acknowledgement:
This work was supported by the Movember Foundation. The funder did not play any role in the study design, collection, analysis or interpretation of data, or in the drafting of this paper. For information, contact Dr. M.J. Roobol: m.roobol@erasmusmc.nl.

Conflict of interest: None to be declared.

Abstract

Background: Careful assessment of reasons for discontinuation of active surveillance (AS) is required for men with prostate cancer (PCa).

Objective: Using Movember's Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3) database, we report on reasons for AS discontinuation.

Design, Setting, and Participants: We compared data from 10,296 men on AS from 21 centres across 12 countries.

Outcome Measurements and Statistical Analysis: Cumulative incidence methods were used to estimate the cumulative incidence rates of AS discontinuation.

Results and Limitation: During 5 years follow-up, 27.5% (95%CI: 26.4%-28.6%) men showed signs of disease progression, 12.8% (95%CI: 12.0%-13.6%) converted to active treatment without evidence of progression, 1.7% (95%CI: 1.5%-2.0%) continued to watchful waiting, and 1.7% (95%CI:1.4%-2.1%) died from other causes. Of the 7,049 who remained on AS, 2,339 had follow-up >5 years, 4,561 had <5 years, and 149 were lost to follow-up. Cumulative incidence of progression was 27.5% (95%CI: 26.4%-28.6%) at 5 years and 38.2% (95%CI: 36.7%-39.9%) at 10 years. A limitation is that not all centres were included due to limited information on reason for discontinuation and limited follow-up.

Conclusion: Our descriptive analyses of current AS practices worldwide showed that 43.6% of men drop out of AS during 5 years follow-up, mainly due to signs of disease progression. Improvements in selection tools for AS are thus needed to correctly allocate men with PCa to AS – which will also reduce discontinuation due to conversion to active treatment without evidence of disease progression.

Patient summary: Our assessment of a worldwide database of men with PCa on AS shows that 43.6% drop out of AS within 5 years, mainly due to signs of disease progression. Better tools are needed to select and monitor men with PCa as part of AS.

Introduction

About two decades ago the concept of active surveillance (AS) was introduced as a management strategy for men with low-risk prostate cancer (PCa) [1]. Men are monitored closely through repeated prostate-specific antigen (PSA) measurements, biopsies, and potentially also Magnetic Resonance Imaging (MRI), with the intention to start curative treatment when their PCa is reclassified to higher risk due to signs of progression (i.e. clinical or pathological) and minimise the harm caused by overtreatment of indolent cancer [2]. However, even though AS has no long-term physical morbidity, studies continue to report that 1.6% to 38% of men opt out of AS, often with no or little evidence of disease progression, within 5 years [3]. Thus, men embarking on AS are likely to transition to an alternative strategy within a decade – which highlights the need for more insight into AS protocols [1, 4].

Careful assessment of reasons for discontinuation of AS is required, especially since treatment pathways for men with low-risk PCa vary by country and are managed differently in various health care systems [5, 6]. It is unclear whether a decrease in health-related quality of life in men on AS precipitates their transition to radical treatment or whether this is driven by the distress over disease progression, physiological symptoms, or the burden of age. Most studies are small and with short follow-up [7-10]. A better understanding of reasons for opting out of AS is thus needed to help define a management strategy for AS.

Hence, in 2014 the Movember Foundation launched the Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3), which covers the largest centralised PCa AS database to date. Its primary goal is to create a global consensus with uniform guidelines on the selection and monitoring of men with low risk PCa [11]. Here, we report on adherence to AS and the reasons for discontinuation by comparing data from 10,296 men on AS from 21 different centres across 12 different countries.

Methods

Study population

Between 2014 and 2016, the global GAP3 database was created by combining patient data from established AS cohorts worldwide. Requirements for participation included, amongst others, ethical approval for sharing digital patient data in a centralized global database, and an active registry of AS patients over the last two years or more, including at least ~50 patients annually. To date, 25 centres from the USA, Canada, Australasia, the UK and Europe fulfilled the requirements for participation and joined the initiative [11] resulting in data for a total of 15,101 men on AS. For the current study, we excluded 3,084 patients from Dublin, MDACC, Toronto and MUSIC as these centres did not distinguish between progression and anxiety events. Furthermore, to ensure as much homogeneity in our AS cohort as possible, we only included men with a Gleason Grade Group of 1, leaving 10,296 patients for the final analysis. Each institution obtained institution ethical approval and signed a Movember End User License Agreement, Access Rights Principles Agreement, and the commonly agreed upon GAP3 analytical plan.

Although there are many variations in existing protocols, most agreed that the most suitable patients for AS are those with age>18, pre-treatment clinical stage T1-T2, serum PSA ≤10 ng/ml, a biopsy Gleason Grade Group of 1 or 2, and a maximum of two tumour-positive biopsy core samples. The AS inclusion criteria for the 25 centres are shown in supplemental Table 1 [11]. Some protocols included PSA density (most often using a cut-off of 0.2 ng/ml), the maximum extent of cancer per core (most often using a cut-off of 50%), life expectancy of >10 years and adequate biopsy sampling as inclusion criteria for AS. An overview of contemporary worldwide AS practices across the world (and included in GAP3) can also be found in the systematic review by Kinsella et al [3] and the cohort profile of the GAP3 database [5].

Following initiation of AS, almost all protocols recommended serial measurements (with a variation in time-intervals) of serum PSA levels, digital rectal examination (DRE) and surveillance biopsy sampling in order to identify pathological progression. Several protocols considered MRI for routine use in AS, again with many differences between recommended frequency. An overview of the AS follow-up protocols of the 25 institutes included in GAP3 is given in Supplemental Table 2 [11].

In addition to baseline criteria for selection and monitoring of AS, the GAP3 database also contains information on discontinuation of AS (i.e. the reasons for stopping AS), and potential following treatments (e.g. radical prostatectomy (RP)) and cause of death. Each centre reports for each patient an event time, defined as the time from his AS initiation to discontinuation of AS due to: 'Convert to watchful waiting', 'Clinical progression', 'Pathological progression', 'Clinical and Pathological progression', 'PSA progression (PSA-DT < 3 years)', 'Other PSA kinetics', 'Patient choice/Anxiety', 'Doctors Anxiety', 'Radiological progression', 'Died', 'Lost to FU', 'Other/Unknown' or 'Still on active surveillance'. These events are defined according to the centres own criteria. We used the following coding for defining signs of disease progression: 'clinical and pathological progression', 'clinical progression', 'other PSA kinetics', 'pathological progression', 'PSA progression', and 'radiological progression'. If the reason for discontinuation was classified as 'other/unknown', but the 'pathological progression status' reported at time of AS discontinuation was 'Gleason Grade Group 3 or higher' or the 'clinical progression status' was 'cT3 or higher' or 'PSA progression status' was 'PSA>20', the reason for discontinuation was also classified as signs of disease progression. The term "sign of disease progression" as used in this manuscript can thus refer to risk reclassification or disease progression as such. Conversion to active treatment without evidence of disease progression includes those patients for whom there was no information on specific discontinuation or disease progression (according to the criteria described above) and for whom specific treatment information was

available, as well as those for whom the reason for discontinuation was registered as 'doctor's anxiety' or 'patient's choice/anxiety'. The distribution of different types of active treatment has been described in detail in our recently published cohort profile [11].

Statistical methods

Descriptive statistics were used to summarize patient characteristics. The cumulative incidence method was used to estimate the rates of each event for discontinuation of AS. Cox proportional hazards regression analyses were used to estimate hazard ratio for various reasons of discontinuation based on age, PSA and number of positive biopsy cores. To account for the heterogeneity between centres, these models used centre as a strata. R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses.

Results

Table 1 shows the distribution of men on AS included in this study according to patient and tumour characteristics, by outcome at 5 years of follow-up. During 5 years follow-up, 27.5% (95%CI: 26.4%-28.6%) men showed signs of disease progression, 12.8% (95%CI: 12.0%-13.6%) converted to active treatment without evidence of progression, 1.7% (95%CI: 1.5%-2.0%) continued to watchful waiting, and 1.7% (95%CI:1.4%-2.1%) died from other causes. Of the 7,049 men who remained on AS during follow-up, 2,339 men had a follow-up of more than 5 years, 4,561 men had less than 5 years of follow-up, and 149 men were lost to follow-up. Hence, at 5 years of follow-up, the cumulative incidence rate of men remaining on AS was 56.4% (95%CI: 55.2%-57.6%) and 43.6% (95%CI: 42.4%-44.8%) were lost to follow-up or discontinued AS. Furthermore, the distribution of outcomes and tumour characteristics per participating centre are shown in Table 2 and ***Supplementary Table 3***.

The cumulative incidence of signs of disease progression was 27.5% (95%CI: 26.4% - 28.6%) at 5 years and 38.2% (95%CI: 36.7% - 39.9%) at 10 years. ***Figure 1*** shows the cumulative incidence for discontinuation based on the different events: signs of progression, conversion to active treatment without evidence of progression, watchful waiting, death, and still on AS. An increase in discontinuation can be observed after one year, with the largest proportion being due to signs of disease progression and conversion to active treatment without evidence of progression. Moreover, it is worth noting that the proportion of men dying from other causes increased gradually throughout the follow-up, which reflects the real world setting of this database. Finally, it can be seen that the proportion of men converting to active treatment without evidence of progression remained stable from about 7 years onwards; a similar trend was observed for conversion to watchful-waiting. To further understand how patient characteristics may affect discontinuation of AS, we generated a forest plot specifically focused on the effects of age (in decade), PSA, and >1 positive biopsy cores (Figure 2). As expected, the strongest positive association is seen for age with transferring to watchful waiting and non-PCa death. Furthermore, >1 positive biopsy core positively associates with progression and non-PCa death.

Figure 3 shows the cumulative incidence for discontinuation for each centre included in the GAP3 database. For all centres, an increase in signs of disease progression was also be observed after one year, but the slope of this increase varied substantially by centre.

Discussion

Based on data from the largest AS database in the world, we observed that after about 5 years of follow-up, about 56.4% of men were still on AS. Substantial variation by centre was observed, but the main reasons for discontinuation were signs of disease progression (27.5% of men) and conversion to active treatment without evidence of disease progression (12.8% of men).

As shown in a recent systematic review by Kinsella et al. many factors influence men's adherence to AS on multiple levels [12]. Their thematic assessment of barriers and facilitators for adherence to AS identified many key themes: (1) patient- and tumour factors (age, co-morbidities, knowledge, education, socioeconomic status, family history, grade, tumour volume, fear of progression/side-effects); (2) family and social support; (3) provider (specialty, communication, attitudes); (4) healthcare organisation (geography, type of practice) and (5) health policy (guidelines, year, awareness)[12]. Interestingly, this systematic review observed that even though a number of studies have shown that emotional distress is relatively high in men at the time of their PC diagnosis [13, 14], anxiety in men on long-term AS has been generally reported as favourably low. More studies have suggested that anxiety in men on AS reduces [15-17] or remains the same over time [8, 17-22].

Our findings of a 43.6% drop-out after about 5 years are in line with previous estimations [23]. However, the proportion of men opting out without evidence for progression was only 12.8%. The variation observed between different institutions shows rather distinct patterns with respect to the proportion of men dropping out due to progression and the proportion of men dropping out due to conversion to active treatment without evidence of disease progression. However, part of the reason why the proportion of drop out due to conversion to active treatment without evidence of disease progression was largest in MSKCC, Singapore, Baden and Goteborg may be explained by the fact that their median follow-up was about three to four years as compared to one to two

years in most other centres. Nevertheless, the data from other centres with also lengthier follow-up such as Hopkins, Valencia and UCSF still showed the largest proportion of discontinuation due to disease progression. In this context, it was also interesting to note that the proportion of men converting to active treatment without evidence of progression in our database remained stable after about 7 years. It can be speculated that more anxious men (and clinicians) were more likely to make the decision about discontinuing AS during the first years. It might suggest that more emphasis on education and support is required during these first years on AS [12]. Surprisingly, the proportion of watchful-waiting also stabilised after seven years, which is unexpected as the population is growing older. Again, this observation might be due to different practices across centres.

The rather large proportion of drop-outs due to signs of disease progression also highlights the need for better inclusion/exclusion criteria, better markers of stable disease, and better outcome measures. For instance, a recent review by Nowinski et al. showed the need for novel approaches of classification, including molecular features, to direct therapy for men with low-grade prostate cancer, especially men on AS [24]. They concluded that by combining GWAS data with gene expression and structural rearrangements, risk alleles were identified that could provide a new basis for developing a prognostication tool to guide therapy for men with early prostate cancer [24, 25].

Moreover, the use of MRI as a tool to risk-stratify men with low-risk PCa has been emerging over time. A study by Thurthle et al. evaluated data from 157 men enrolled on AS using a protocol including multiparametric MRI and noted low progression and treatment conversion rates [26]. Changes in mpMRI findings were found to be the principle trigger for detecting progression by imaging alone or pathologically. In addition, the recent findings of the PROMIS trial, which was based on men with PSA concentrations up to 15 ng/mL, with no previous

biopsy, have shown us that MRI identified nearly all men with clinically significant prostate cancer (93%) versus the current practice standard (trans-rectal biopsy), which identified only 48% [27]. The endotype generated by a positive MRI was positively associated with grade and volume and contained cancer in most cases (Likert ≥4=92%; Likert≥3=60%). An update of the current Movember GAP3 database with information on MRI images will hence provide us more insight into the use of MRI as a selection and monitoring tool for AS.

In addition to genetics and MRI, several studies have also investigated the use of serum biomarkers as a tool to monitor men on AS. However, a recent systematic review by Loeb and Tosoian [28] concluded that very few markers have longitudinal results available yet for men on AS – indicating an important area for future research where the GAP3 database will be able to contribute. Furthermore, simple changes in clinical assessment have been proposed as a strategy to reduce rates of discontinuation of AS. Bokhorst et al. has, for example, shown that the number of positive biopsies should no longer be used to trigger immediate active treatment, but rather indicate further investigation to confirm the suspicion of higher risk disease [29].

The GAP3 database is a unique resource covering data from all over the world. Some limitations exist, resulting in not all centres being included in these analyses due to the lack of information on reason for discontinuation and limited follow up. However, even after a follow-up of 5 years we could already observe clear patterns with respect to reasons for discontinuation. The heterogeneity in study protocols and data collection across centres can be seen as a limitation, however we would like to argue that it is this real world setting that adds value to our understanding of AS. As outlined by PIONEER, the big prostate cancer data consortium of the European Association of Urology, combining and analysing the patient records of men diagnosed with prostate cancer can enable healthcare systems to provide more efficient outcome-driven patient-centred interventions [30]. By providing data from a wide variety of centres, GAP3

has the power to transform the perspective of all relevant stakeholders. Movember has recently also allocated additional funding to maintain the database and update the clinical data annually thereby prolonging follow up time. Furthermore, this provides the opportunity to collect evidence on imaging (MRI), molecular (genomics) markers, patient-related outcomes and more. In addition, it is worth noting that qualitative data on its own will not be sufficient to answer the question about adherence to AS – there is a need to combine our observations with qualitative studies to truly understand patterns of discontinuation [12]. Given the available data on the natural course of low risk disease, the question about whether active monitoring leads to better outcome and benefit whilst avoiding missing the window of cure in case of reclassification/progression is crucial.

Conclusion

Our descriptive analyses of current AS practices around the world showed that about 43.6% of men drop out of AS after 5 years, mainly due to signs of disease progression – about 12.8% of drop-outs were due to conversion to active treatment without evidence of progression. Improvements in selection tools for AS (e.g. biomarkers or MRI) are thus needed to correctly allocate men with PCa to AS – which in turn will also reduce discontinuation due to conversion to active treatment without evidence of disease progression.

References

[1] Albertsen PC. Active Surveillance: A Ten-year Journey. Eur Urol. 2016.
[2] Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol. 2012;62:976-83.
[3] Kinsella N, Helleman J, Bruinsma S, Carlsson S, Cahill D, Brown C, et al. Active surveillance for prostate cancer: a systematic review of contemporary worldwide practices. Transl Androl Urol. 2018;7:83-97.
[4] Bokhorst LP, Alberts AR, Rannikko A, Valdagni R, Pickles T, Kakehi Y, et al. Compliance Rates with the Prostate Cancer Research International Active Surveillance (PRIAS) Protocol and Disease Reclassification in Noncompliers. Eur Urol. 2015;68:814-21.
[5] Bruinsma SM, Bangma CH, Carroll PR, Leapman MS, Rannikko A, Petrides N, et al. Active surveillance for prostate cancer: a narrative review of clinical guidelines. Nat Rev Urol. 2016;13:151-67.
[6] Chen RC, Rumble RB, Loblaw DA, Finelli A, Ehdaie B, Cooperberg MR, et al. Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol. 2016;34:2182-90.
[7] van den Bergh RC, Essink-Bot ML, Roobol MJ, Wolters T, Schroder FH, Bangma CH, et al. Anxiety and distress during active surveillance for early prostate cancer. Cancer. 2009;115:3868-78.
[8] Wilcox C GD, Louie-Johnsun Anxiety and health related quality of life (HRQL) in patients undergoing active surveillance of prostate cancer in an Australian centre. BJU Int. 2014;113:64-8.
[9] Bergman J, Litwin MS. Quality of life in men undergoing active surveillance for localized prostate cancer. Journal of the National Cancer Institute Monographs. 2012;2012:242-9.
[10] Jiwa M, Halkett G, Meng X, Pillai V, Berg M, Shaw T. Supporting patients treated for prostate cancer: a video vignette study with an email-based educational program in general practice. Journal of medical Internet research. 2014;16:e63.
[11] Bruinsma SM, Zhang L, Roobol MJ, Bangma CH, Steyerberg EW, Nieboer D, et al. The Movember Foundation's GAP3 cohort: a profile of the largest global prostate cancer active surveillance database to date. BJU Int. 2017.
[12] Kinsella N, Stattin P, Cahill D, Brown C, Bill-Axelson A, Bratt O, et al. Factors influencing men's choice of and adherence to active surveillance for low-risk prostate cancer: A mixed-methods systematic review. European Urology Supplements. 2018;In press.
[13] Korfage I, Essink-Bot M-L, Janssens A, Schröder F, De Koning H. Anxiety and depression after prostate cancer diagnosis and treatment: 5-year follow-up. British journal of cancer. 2006;94:1093-8.
[14] Orom H, Underwood W, III, Biddle C. Emotional Distress Increases the Likelihood of Undergoing Surgery among Men with Localized Prostate Cancer. The Journal of Urology. 2017;197:350-5.
[15] Vasarainen H, Lokman U, Ruutu M, Taari K, Rannikko A. Prostate cancer active surveillance and health-related quality of life: results of the Finnish arm of the prospective trial. BJU Int. 2012;109:1614-9.

[16] Vanagas G, Mickevičienė A, Ulys A. Does quality of life of prostate cancer patients differ by stage and treatment? Scandinavian Journal of Public Health. 2013;41:58-64.
[17] van den Bergh RC, Essink-Bot ML, Roobol MJ, Schroder FH, Bangma CH, Steyerberg EW. Do anxiety and distress increase during active surveillance for low risk prostate cancer? J Urol. 2010;183:1786-91.
[18] Burnet KL, Parker C, Dearnaley D, Brewin CR, Watson M. Does active surveillance for men with localized prostate cancer carry psychological morbidity? BJU Int. 2007;100:540-3.
[19] Davison BJ, Goldenberg SL. Patient acceptance of active surveillance as a treatment option for low-risk prostate cancer. BJU Int. 2011;108:1787-93.
[20] Bellardita L, Rancati T, Alvisi MF, Villani D, Magnani T, Marenghi C, et al. Predictors of health-related quality of life and adjustment to prostate cancer during active surveillance. Eur Urol. 2013;64:30-6.
[21] Punnen S, Cowan JE, Dunn LB, Shumay DM, Carroll PR, Cooperberg MR. A longitudinal study of anxiety, depression and distress as predictors of sexual and urinary quality of life in men with prostate cancer. BJU International. 2013;112:E67-E75.
[22] Anderson J, Burney S, Brooker JE, Ricciardelli LA, Fletcher JM, Satasivam P, et al. Anxiety in the management of localised prostate cancer by active surveillance. BJU Int. 2014;114 Suppl 1:55-61.
[23] Dall'Era MA, Cooperberg MR, Chan JM, Davies BJ, Albertsen PC, Klotz LH, et al. Active surveillance for early-stage prostate cancer: review of the current literature. Cancer. 2008;112:1650-9.
[24] Nowinski S, Santaolalla A, O'Leary B, Loda M, Mirchandani A, Emberton M, et al. Systematic identification of functionally relevant risk alleles to stratify aggressive versus indolent prostate cancer. Oncotarget. 2018;9:12812-24.
[25] Cozar JM, Robles-Fernandez I, Martinez-Gonzalez LJ, Pascual-Geler M, Rodriguez-Martinez A, Serrano MJ, et al. Genetic markers a landscape in prostate cancer. Mutat Res. 2018;775:1-10.
[26] Thurtle D, Barrett T, Thankappan-Nair V, Koo B, Warren A, Kastner C, et al. Progression and treatment rates using an active surveillance protocol incorporating image-guided baseline biopsies and multiparametric magnetic resonance imaging monitoring for men with favourable-risk prostate cancer. BJU Int. 2018.
[27] Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389:815-22.
[28] Loeb S, Tosoian JJ. Biomarkers in active surveillance. Transl Androl Urol. 2018;7:155-9.
[29] Bokhorst LP, Valdagni R, Rannikko A, Kakehi Y, Pickles T, Bangma CH, et al. A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. Eur Urol. 2016;70:954-60.
[30] European Association of U. PIONEER: the European Network of Excellence for Big Data in Prostate Cancer. 2018.

Tables

Table 1. Distribution of men on AS according to patient and tumour characteristics, by outcome following AS at 5 years of follow-up. The median and the inter-quartile range are provided for each variable.

Variable	Censor or Still on AS (N = 7,049)	Progression-Treatment (N = 2,061)	Convert to active treatment without evidence of progression (N = 952)	Watchful Waiting (N=118)	Other cause of Death (N = 116)	p-value*
Years on AS	3.3 (1.4, 5.8)	1.4 (1.1, 2.5)	1.6 (1.0, 2.7)	1.7 (1.2, 3.1)	2.3 (1.5, 3.4)	<0.01
Year of Diagnosis	2010 (2007, 2013)	2010 (2007, 2011)	2008 (2004, 2010)	2010 (2009, 2010)	2007 (2003, 2010)	<0.01
Age at start of AS (years)	65 (60, 69)	65 (61, 69)	65 (60, 69)	72 (65, 75)	69 (65, 73)	<0.01
PSA at start of AS (ng/ml)	5.3 (3.9, 7.2)	5.4 (4.2, 7.0)	5.6 (4.2, 7.3)	5.9 (4.5, 7.5)	6.4 (4.2, 9.1)	0.01
Number of biopsy cores with PCa	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	<0.01

* Kruskal-Wallis rank sum test

Table 2. Number of patients from each centre in GAP3 at 5 years of follow-up.

Centre	Still on AS	Still on AS, follow-up < 5 years	Lost to follow-up	Progression	Converted to Active Treatment	Watchful Waiting	Death from other causes	Total
Atlanta	5	41	0	2	0	0	0	48
Baden	44	52	0	22	24	2	1	145
Calgary	82	346	0	80	30	0	0	538
Cambridge	21	162	14	18	7	1	1	224
Erasmus MC	49	18	3	33	4	5	0	112
PRIAS centres	149	1368	26	392	136	51	13	2135
Gothenburg	293	147	1	111	142	0	43	737
Helsinki	58	97	1	97	9	17	3	282
Hopkins	461	315	91	400	141	0	9	1417
Kagawa	29	2	1	45	19	3	5	104
Lille	4	94	10	36	10	0	1	155
London-KCL	58	43	0	83	8	0	2	194
London-UCL	30	230	0	0	10	2	0	272
Malmo	10	90	1	19	4	1	1	126
Melbourne	53	114	0	63	3	3	0	236
Milan	102	287	0	245	51	23	2	710
MSKCC	443	344	0	56	190	0	16	1049
Seoul	0	33	0	2	1	0	0	36
Singapore	21	93	0	20	46	0	1	181
UCSF	405	487	0	262	94	0	11	1259
Valencia	22	149	0	61	21	10	5	268
Vancouver	0	49	1	14	2	0	2	68
Total	2339	4561	149	2061	952	118	116	10296

Figures

Figure 1. Cumulative incidence of discontinuation of active surveillance over time.

Figure 2. Forest plot showing the association between age, PSA, positive biopsy cores and different reasons of discontinuation of active surveillance.

Figure 3. Cumulative incidence of discontinuation of active surveillance over time for each centre in the GAP3 database.

Supplementary data

Institute abbreviations:
Monash - Monash University and Epworth Health, Melbourne, Australia; Kagawa - Kagawa University Faculty of Medicine, Kagawa, Japan; Singapore - Singapore General Hospital, Singapore; Seoul - Gangnam Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; Helsinki - Helsinki University Central Hospital, Helsinki, Finland; Gothenburg - Sahlgrenska University Hospital, Göteborg, Sweden; Malmö - Skåne University Hospital, Malmö, Sweden; Dublin - University College Dublin, Dublin , Ireland; Erasmus - Erasmus Medical Center, Rotterdam, the Netherlands; Lille - Lille University Hospital Center, Lille, France; Baden - Kantonsspital Baden, Baden, Switzerland; Milan - Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Valencia - Instituto Valenciano de Oncología, Valencia, Spain; Cambridge - Cambridge University Hospitals NHS Trust, Cambridge, United Kingdom; KCL - King's College London, London, UK & Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; UCL - University College London & University College London Hospitals Trust, London, United Kingdom; Vancouver - University of British Columbia , BC Cancer Agency, Vancouver, Canada); Calgary - University of Calgary, Southern Alberta Institute of Urology, Calgary, Canada; Toronto - University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Canada; MSKCC - Memorial Sloan Kettering Cancer Center, New York, USA; Hopkins - Johns Hopkins University, Baltimore, USA; MUSIC - University of Michigan and Michigan Urological Surgery Improvement Collaborative, Michigan, USA; Emory - Emory University School of Medicine, Winship Cancer Institute, Atlanta, USA; MD Anderson - MD Anderson Cancer Centre, Houston, USA; UCSF - University of California, San Francisco, San Francisco, USA

Table S1. Inclusion criteria for Active Surveillance for each centre included in GAP3.

NR=not reported

Center	Age (years)	Clinical stage	Serum PSA (ng/ml)	Biopsy Gleason Score	Serum PSA density (ng/ml/g)	Positive cores (n)	Min- max extent cancer per cores
Asia/Australia							
Monash	>18	T1c or T2	≤10	3+3=6 or 3+4=7, up to 20% of Pattern 4	<0.2	1-2	≤5 mm per core (± equal 25% of a core)
Kagawa	50-80	T1cN0M0	≤20	≤3+3=6	NR	1-2 per 6-12 systematic biopsy cores	≤50%
Singapore	>18	T1-T2	<10	3+3	NR	NR	≤50%
Seoul	>18	T1-T2a	≤10	≤7	NR	<2	NR
Europe							
Helsinki	NR	≤T2	≤10	≤6	<0.2	1-2	NR
Gothenburg	>18	T1	<10	3+3=6	NR	NR	NR
Malmö	>18	T1c or T2	≤10	3+3=6 or 3+4	<0.2	1-2	NR
Dublin	>18	T1-T2a	<10	≤6	NR	NR	NR
Erasmus	NR	≤T2	≤10	≤6	<0.2	1-2	NR
Lille	>18	T1c	≤15	3+3=6 or 3+4	NR	≤3	1-5
Baden	>18	T1a-T1c (T2a)	<10	≤6 (3+3)	NR	≤2	≤5 mm/core
Milan	>18	PRIAS: T1c-T2a; SAINT: T1c-T2a; T2b if ≤0.5 mL tumor volume and negative peripheral zone biopsy	≤10	3+3=6	PRIAS: <0.20; SAINT: NR	PRIAS: ≤2; ≤15% if saturation biopsy; No restriction if GS 3+3 fusion biopsy or negative RMmp; SAINT: ≤3 and ≤25% of total cores	PRIAS: X; SAINT: ≤50%
Valencia	<80	T1a, T1b, T1c	≤10	≤6 or 3+4 (3+4 for men >70 years old)	<0.2	≤2	33% to ≤50%
UK							
Cambridge	50-75	T1-T2a	≤10	≤6; 7 based on patient-clinical discussion	NR	NR	NR
KCL	>18	T1a-T1b, T2	≤15	≤6 or ≤3+4=7	NR	NR	NR
UCL	>18	NR	<20	Up to Gleason 7	No specific limit	Targeted biopsy strategy used	NR
United States							
MSKCC	>18	NR	NR	6	NR	NR	≤50%
Hopkins	>40	T1c, T2a	<10 (for men not meeting VLR criteria)	3+3=6	<0.15 to define VLR, and <0.1if PSA over 10ng/mL	2 or less	50% or less of any core, unless unilateral disease then NR
MUSIC	>18	T1-T2b	≤10	<7	NR	≤1/3 or all cores involved	≤50%
Emory	>18	T1-T2	<10	a) 3+3=6 b) 3+4=7 with <10% of Pattern 4 if age >70	<0.15	a) <6 if 3+3=6 b) <3 if 3+4=7	<50% any core
MD Anderson	>18	T1-T2	<4 <4	3+3=6 3+4=7	NR	≤1with <3mm tumor ≤1with <2mm tumor	NR
UCSF	>18	≤T2	≤10	≤6	NR	NR	NR
Canada							
Calgary	<59 (stage I); >60 (stage II)	≤T2	NR	6 (stage I or II): or 3+4 stage II	NR	≤3 Stage I <6 Stage II	<50%
Toronto	>18	NR	≤10 10-20	≤6 3+4	NR	NR	<30%
Vancouver	NR	≤T2	≤10	≤6	<0.2	1-2	Maximum of 50% or 5mm of PCa in a single core

Table S2. Follow-up protocol for Active Surveillance for each centre included in GAP3.

PSADT=PSA doubling time; PSAV=PSA velocity; DRE=Digital rectal exam; mpMRI=multi-parametric Magnetic resonance imaging; NR=not reported

Center	Serum PSA	PSA Kinetics (PSAD/PSAV)	DRE	Biopsy	mpMRI
Asia/Australia					
Monash	Every 3 months	NR	Every 6 months	After months 12, 48, and 84	NR
Kagawa	Every 3 months for the first 6 months, then every 3 months	NR	Every 12 months	Every 12 months	NR
Singapore	3-6 monthly for the first 2 years, then 6-12 monthly thereafter	Every 12 months	Every 12 months	Every 12 months	Every 12 months
Seoul	Every 3 months	NR	NR	Considered if mpMRI result is changed	Every 12 months
Europe					
Helsinki	Every 3 months	Every 6 months	Every 6 months	After months 12, 48, and 84	NR
Gothenburg	Every 3-6 months	NR	Every 6-12 months	Every 2-3 years	NR
Malmö	Every 3 months	NR	Every 6 months	After months 12, 48, and 84	NR
Dublin	NR	NR	NR	1year, than every other year.	NR
Erasmus	Every 3 months	Every 6 months	Every 6 months	After months 12, 48, and 84	NR
Lille	Every 6 months	NR	Every 12 months	At month 12	At month 12
Baden	Every 6 months	NR	Every 6 months	Every 24 months	NR
Milan	Every 3 months	NR	Every 6 months	Every 12 months for the first 2 years and then every 24 months	NR
Valencia	Every 6 months	NR	Every 6 months	Month 24 from start on AS, then every 3 years if no progression	NR
UK					
Cambridge	Every 3 months	Every 12 months	NR	At Months 12, 36, 60	At Months 12, 36, 60
KCL	Every 6 months	Every 12 months	Every 12 months	NR	Every 12 months
UCL	3-4 monthly in 1year; 6 monthly after that	NR	Not routinely done	For men where there is a change in MRI and uncertainty about converting to active treatment	At baseline and 12 months for all men. After that, dependent on risk factors including MRI findings, PSA density and Gleason score.
United States					
MSKCC	Every 6 months	NR	Every 6 months	Every 3 years	Every 18 months
Hopkins	Every 6 months	NR	Every 6 months	Every 12 months	NR
MUSIC	Every 3-6 months	NR	Every 12 months	Every other year	Every other year; confirmatory test in first 3-4 months
Emory	Every 6 months	NR	Every 12 months	Every 12 months	Annually for the first 3 years, then final scheduled at 5 years
MD Anderson	Every 6 months	NR	Every 6 months	Every 12 months	Every 12 months
UCSF	Every 3 months	NR	Every 6 months	Every 12-24 months	NR
Canada					
Vancouver	Every 3 months	Every 6 months	Every 6 months	After months 12, 48, and 84	NR
Calgary	Every 6 months	NR	Every 6 months	At year 1, then every 2 years	When PSA>10
Toronto	Every 3 months until 2 years, then every 6 months	Every 12 months	Every 6 months	At Year 1, 4, 7, 10, and 15	Every 12 months

Table S3. Patients and tumour characteristics of each centre at 5 years of follow-up.

Variable	Atlanta	Baden	Calgary	Cambridge	Erasmus MC	PRIAS centres
Years on AS (Median, range)	1.0 (0, 8.0)	3.5 (0, 11.5)	2.3 (0, 8.9)	2.1 (0, 9.6)	4.6 (0, 13.8)	1.5 (0, 8.5)
Year of Diagnosis (Median, range)	2013 (2006, 2015)	2009 (2000, 2015)	2013 (2007, 2016)	2012 (2003, 2015)	2008 (2000, 2014)	2011 (2004, 2015)
Age at start of AS (years; Median, range)	66 (41, 79)	67 (45, 78)	62 (42, 79)	66 (43, 79)	67 (49, 75)	66 (42, 79)
PSA at start of AS (ng/ml; Median, range)	5.6 (1.8, 11)	4.7 (0.5, 19.6)	4.3 (0.2, 24.9)	6.8 (0.5, 29.2)	4.6 (0.3, 11)	5.8 (0.3, 16.7)
Number of biopsy cores with PCa (Median, range)	1 (0, 7)	NA	1 (0, 8)	1 (0, 20)	1 (0, 5)	1 (0, 10)
Variable	**Gothenburg**	**Helsinki**	**Hopkins**	**Kagawa**	**Lille**	**London-KCL**
Years on AS (Median, range)	3.8 (0, 17.4)	2.5 (0, 8)	3.1 (0, 18.8)	2.3 (0, 10.1)	1.4 (0, 6.7)	3 (0, 12)
Year of Diagnosis (Median, range)	2005 (1995, 2015)	2010 (2006, 2016)	2008 (1992, 2014)	2003 (2002, 2003)	2012 (2007, 2015)	2009 (2003, 2012)
Age at start of AS(years; Median, range)	67 (51, 79)	63 (41, 78)	66 (41, 79)	70 (55, 79)	65 (43, 79)	63 (41, 79)
PSA at start of AS (ng/ml; Median, range)	4.6 (0.9, 29)	5.6 (0.9, 10)	4.8 (0.2, 27.6)	6.5 (2.1, 15.9)	6.5 (1.1, 25)	6 (1, 27)
Number of biopsy cores with PCa (Median, range)	1 (1, 10)	1 (0, 9)	1 (0, 11)	1 (0, 7)	1 (0, 15)	2 (0, 18)
Variable	**London-UCL**	**Malmo**	**Melbourne**	**Milan**	**MSKCC**	**Seoul**
Years on AS (Median, range)	0 (0, 8)	1.7 (0, 6.7)	2.5 (0, 10)	2.1 (0, 9.9)	4.4 (0, 16.8)	1.3 (0.1, 4.2)
Year of Diagnosis (Median, range)	2009 (2001, 2013)	2012 (2007, 2014)	2009 (2003, 2013)	2011 (2004, 2015)	2008 (1993, 2011)	2015 (2011, 2016)
Age at start of AS (years; Median, range)	62 (44, 78)	66 (48, 78)	63 (45, 79)	66 (42, 79)	63 (41, 79)	68 (50, 79)
PSA at start of AS (ng/ml; Median, range)	6.3 (0.4, 24.6)	5.1 (2.4, 10.7)	5.9 (0.3, 26.1)	5.7 (0.3, 22.7)	4.6 (0, 22)	5.0 (0.7, 20.6)
Number of biopsy cores with PCa (Median, range)	2 (1, 6)	1 (0, 5)	2 (0, 15)	1 (0, 8)	1 (0, 13)	NA
Variable	**Singapore**	**UCSF**	**Valencia**	**Vancouver**		
Years on AS (Median, range)	2.5 (0.5, 9.1)	3.3 (0.5, 20.4)	1.6 (0, 13.6)	1.8 (0, 4.4)		
Year of Diagnosis (Median, range)	2011 (2000, 2014)	2009 (1993, 2015)	2012 (2001, 2016)	2007 (2004, 2009)		
Age at start of AS (years; Median, range)	66 (47, 79)	62 (41, 79)	66 (41, 79)	67 (49, 77)		
PSA at start of AS (ng/ml; Median, range)	6.3 (0.1, 29.3)	5.4 (0.3, 28.2)	5.4 (0.9, 28.9)	5.4 (0.7, 11.6)		
Number of biopsy cores with PCa (Median, range)	1 (0, 15)	2 (0, 16)	1 (0, 12)	1 (0, 4)		

APENDIX A

***Members of The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) consortium**